Menopausal hormone therapy and cardiovascular risk

AUTHORS: Kathryn A Martin, MD, Robert S Rosenson, MD
SECTION EDITORS: Peter J Snyder, MD, Robert L Barbieri, MD, Juan Carlos Kaski, DSc, MD, DM (Hons), FRCP, FESC, FACC, FAHA
DEPUTY EDITOR: Jean E Mulder, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Feb 2025.**
This topic last updated: **Apr 28, 2023.**

INTRODUCTION

Normal women have menopause at a mean age of 51 years, with 95 percent becoming menopausal between the ages of 45 to 55 years. Estrogen is the most effective treatment available for relief of menopausal symptoms, most importantly hot flashes. Menopausal hormone therapy (MHT; estrogen alone or combined with a progestin) is currently indicated for management of menopausal symptoms. Long-term use for prevention of disease is no longer recommended.

The impact of MHT on cardiovascular risk will be reviewed here. The discussion will include both cardiovascular outcomes and the effect of estrogen therapy on serum lipid values, blood pressure, and body weight. Other aspects of estrogen therapy are reviewed in detail elsewhere. (See "Menopausal hormone therapy: Benefits and risks" and "Menopausal hormone therapy in the prevention and treatment of osteoporosis" and "Menopausal hormone therapy and the risk of breast cancer" and "Treatment of menopausal symptoms with hormone therapy".)

CORONARY HEART DISEASE

Although initial observational studies suggested benefit from menopausal hormone therapy (MHT) for both primary and secondary prevention of coronary heart disease (CHD), this was not confirmed in subsequent large trials. Factors including the older age of the subjects in the Women's Health Initiative (WHI) population, as well as the estrogen type, route of administration, and dose may play a role [1].

Cardiovascular effects of estrogen — A number of effects of estrogen could affect the risk of cardiovascular disease. However, it is not known how these effects influence the overall risk of CHD with MHT [2,3]. Examples of potential beneficial effects of estrogen include:

- An improvement in lipid profiles, primarily with oral estrogens. (See 'Lipids' below.)
- Enhanced endothelial function, which may occur in young healthy women, but not older postmenopausal women with coronary disease [4,5].
- Improved insulin sensitivity, although data are inconsistent.

Examples of potential adverse effects include:

- An increase in serum triglyceride concentrations with oral estrogens. (See 'Lipids' below.)
- Prothrombotic effects including a reduction in factor VII and antithrombin III with oral estrogen (less affected by transdermal estrogen) [6].
- An increase in hepatic synthesis of vascular inflammatory markers such as C-reactive protein (CRP) (primarily oral preparations) [7].

Effects of progestins — Synthetic progestins, such as medroxyprogesterone acetate (the progestin used in the WHI trial and Heart and Estrogen/Progestin Replacement Study [HERS] described below), may negate some of the effects of estrogen on lipids and endothelial function [4,8]. Natural progesterone has been less well studied but does not appear to negate the effects of estrogen on serum lipids. (See 'Lipids' below.)

Both unopposed conjugated estrogen and combined conjugated estrogen-progestin therapy increase CRP concentrations. In one study, the increase in CRP was positively or negatively correlated with interleukin-6 (IL-6) with combined estrogen-progestin therapy or unopposed estrogen, respectively [9]. This suggests a noninflammatory pathway for stimulation of CRP with unopposed estrogen, but an inflammatory one when progestin is added.

Primary prevention — Beginning in the late 1980s, there was a shift from prescribing short-term estrogen therapy for menopausal women for symptoms to prescribing it long-term (more than five years) for prevention of disease, particularly CHD. This prevention strategy was based on over 30 observational studies, almost all of which demonstrated a striking protective effect of estrogen on the heart [10-12]. In addition to the observational data, angiographic and autopsy studies suggested an antiatherogenic effect of estrogen [13,14].

However, initial publications from the WHI trial suggested that MHT was not effective for primary prevention of CHD [15,16]. The WHI trial was a set of clinical trials, including two estrogen therapy trials, in healthy postmenopausal women aged 50 to 79 years.

One of the trials (combined continuous estrogen-progestin regimen [conjugated estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg/day] versus placebo in over 16,000 women) was discontinued three years early due to an increased risk of breast cancer, stroke, CHD, and venous thromboembolism (VTE) over an average follow-up of 5.2 years [15]. Although there were significant benefits (reduction in risk of fractures and colon cancer), there was concern that the risks of estrogen-progestin therapy outweighed the benefits in some women.

The WHI unopposed estrogen (conjugated estrogen 0.625 mg) versus placebo trial in nearly 11,000 women who had undergone hysterectomy (and therefore did not require a progestin) was also discontinued (one year early), due to an increased risk of stroke and a calculation that suggested no overall health benefit [16]. (See "Menopausal hormone therapy: Benefits and risks".)

Combined estrogen-progestin — In the initial reports from the WHI, the hazard ratio (HR) for CHD (nonfatal myocardial infarction or death due to CHD) in the overall cohort taking combined estrogen-progestin trial was 1.24 (95% CI 1.0-1.5) [17]. However, subsequent analysis suggests that the increased risk may be confined to older women. (See 'Timing of exposure' below.)

Other factors, including body mass index (BMI), presence of vasomotor symptoms, additional coronary risk factors (including diabetes, hypertension, family history, and smoking), aspirin or statin use, and CRP were not significantly related to CHD risk with hormone therapy (HT). Biochemical predictors of risk and the possible effect of age and years from menopause are discussed below. (See 'Predictors of risk' below and 'Timing of exposure' below.)

There was a significant increase in stroke and VTE (figure 1 and figure 2). (See 'Stroke' below and 'Venous thromboembolism' below.)

The risk of breast cancer was slightly increased, but the absolute excess risk was very small. The risk of fracture and colon cancer was decreased, as discussed elsewhere. (See "Menopausal hormone therapy and the risk of breast cancer" and "Menopausal hormone therapy in the prevention and treatment of osteoporosis" and "Menopausal hormone therapy: Benefits and risks".)

The absolute risk of any adverse event (breast cancer, CHD, stroke, or VTE) occurring in an individual was **extremely low** (19 additional events per year per 10,000 women with MHT

versus placebo).

A second, multicenter trial (Women's International Study of Long-Duration Oestrogen After Menopause [WISDOM]), similar in design and patient population to the WHI, enrolled 5692 women but was discontinued after the publication of the early results from the WHI [18]. However, after a median follow-up of 12 months, an excess risk of CHD events and VTE, but not stroke, was observed in the overall cohort receiving combined estrogen-progestin group compared with placebo. There were too few events to analyze risk based upon patient age or years from menopause. (See 'Timing of exposure' below.)

Unopposed estrogen — Unlike the excess overall CHD risk observed in the combined estrogen-progestin trial, the WHI reported an HR for CHD of 0.95 (95% CI 0.70-1.16) in the unopposed estrogen trial [16]. There was a suggestion of a protective effect in the younger women (ages 50 to 59 years) [19]. (See 'Timing of exposure' below.)

The discrepancies in CHD risk between the unopposed estrogen and the combined estrogen-progestin trials suggest that the progestin played an important role in the increased CHD risk seen with combined therapy [20].

Other effects of unopposed estrogen included an increase in stroke and venous thromboembolic complications (similar to that seen with combined therapy). (See 'Stroke' below and 'Venous thromboembolism' below and "Menopausal hormone therapy: Benefits and risks".)

Predictors of risk — Predictors of CHD risk were subsequently examined in a nested, case-control study of 359 CHD cases and 820 controls from the combined trials with the following results [21]:

- After adjustment for the presence of cardiovascular disease, statin therapy, and diabetes mellitus, baseline levels of several thrombotic, inflammatory, and lipid biomarkers (including factor VIII, D-dimer, IL-6, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides) were associated with CHD events.

- Only LDL cholesterol modified the effect of treatment, as women with high baseline LDL cholesterol concentrations were at greater risk for CHD if given MHT.

- Combined therapy affected levels of several biomarkers (increases in CRP, HDL, triglycerides, and decreases in LDL), but the changes were not associated with a change in CHD risk.

Timing of exposure — Data from a primate model [22], two observational studies in postmenopausal women [23,24], a meta-analysis of clinical trials [25], a coronary angiographic study [26], and secondary analyses from the WHI [19,27] all suggest that the timing of exposure to MHT is an important factor in determining subsequent cardiovascular risk. The use of MHT in the early menopausal years does not appear to be associated with an excess risk of CHD when compared with older postmenopausal women. This has been referred to as the "timing hypothesis."

The WHI population was an older population (mean age 63 years) when compared with most observational studies; the older age at the time of MHT initiation would be expected to be associated with more subclinical atherosclerosis at baseline, with advanced or complex atherosclerotic lesions that may be more susceptible to the prothrombotic, proinflammatory effects of estrogen. In contrast, starting MHT soon after menopause may not cause harm (or may possibly be beneficial) because advanced, unstable atherosclerotic plaques have not yet formed. This hypothesis is supported by the following observations from the WHI:

- In a combined analysis of the two WHI HT trials, women who started MHT closer to menopause appeared to have a lower risk of CHD compared with women further from menopause [27].
  - For the age groups of 50 to 59 years, 60 to 69 years, and 70 to 79 years, the HRs for CHD were 0.93, 0.98, and 1.26, with absolute excess risks of -2, -1, and +19 per 10,000 person-years, respectively. This trend did not reach statistical significance.
  - For women <10, 10 to 19, or ≥20 years since menopause, HRs for CHD were 0.76, 1.10, and 1.28, with absolute excess risks of -6, +4, and +17 per 10,000 person-years, respectively (p for trend = 0.02).
- In the WHI-Coronary Artery Calcium Study, an ancillary substudy performed in younger women ages 50 to 59 years, evidence of subclinical atherosclerosis (as measured by coronary-artery calcium scores on electron beam computed tomography [CT]) was lower in those assigned to unopposed estrogen when compared with placebo [28].
- The Kronos Early Estrogen Prevention Study (KEEPS), a four-year, randomized, double-blind, placebo-controlled trial in 727 women ages 45 to 54 years, reported that when combined with cyclical monthly oral progesterone, oral conjugated estrogen (0.45 mg daily) or transdermal estradiol (50 mcg daily) reduced menopausal symptoms and improved some markers of cardiovascular disease (increased HDL, decreased LDL with oral estrogen; decreased insulin resistance with transdermal estrogen) [29]. However, HT had no effect of surrogate markers of atherosclerosis progression (coronary artery calcium and carotid

intima-medial thickness [CIMT]) when compared with placebo. The authors suggest that the lack of protective effect could be due to the young age and low risk profile of the subjects, the short duration of the trial, and the low doses of estrogen used.

- In The Early versus Late Intervention Trial with Estradiol (ELITE), 643 postmenopausal women, stratified according to time since menopause (<6 or >10 years; early versus late, respectively), received oral estradiol (with progesterone for women with a uterus) or placebo for a median of five years [30]. Progression of subclinical atherosclerosis (measured as CIMT) was slower than placebo in the early intervention group, while rates of progression were similar to placebo in the late intervention group. Estradiol had no effect on CT coronary artery calcium in either the early or late intervention group.

- A 2015 meta-analysis of 19 trials of oral (including the WHI), but not transdermal, MHT in over 40,000 postmenopausal women performed subgroup analyses in women who started MHT less than 10 years after menopause [31] (see "Menopausal hormone therapy: Benefits and risks", section on 'Younger, postmenopausal women'). A lower risk of CHD and mortality were reported. A 2017 meta-analysis of similar trials concluded that the risks of long-term use of MHT for prevention of chronic disease outweighed any benefits [32].

Most now agree that age or time since menopause influences the risk-benefit ratio associated with HT, most importantly with respect to CHD. The use of unopposed estrogen may be more favorable than combined estrogen-progestin (at least for the synthetic progestin used in the WHI, medroxyprogesterone acetate). In spite of these reassuring data, MHT is indicated only for management of menopausal symptoms in younger women, not for primary prevention of CHD [32,33]. For women who are recently menopausal, the improvement in vasomotor symptoms must still be weighed against other potential risks of treatment, but coronary disease is not usually a major factor in the equation.

Other specific recommendations regarding estrogen therapy are discussed elsewhere. (See "Treatment of menopausal symptoms with hormone therapy".)

Type of estrogen — The type of estrogen may also be important in determining risk. Both the WHI and the HERS trials employed conjugated equine estrogen-progestin therapy (see 'Secondary prevention' below). In comparison, the Estrogen in Prevention of Atherosclerosis Trial (EPAT) randomly assigned 222 healthy, postmenopausal women to unopposed oral 17-beta-estradiol (1 mg/day) or placebo [13]. Estradiol therapy was associated with a decreased risk of atherosclerosis (as measured by CIMT). Higher serum concentrations of sex hormone-binding globulin (SHBG) and estrogen were inversely correlated with CIMT progression after

controlling for age and BMI. The association was partially mediated by beneficial effects on lipids [34].

However, 17-beta-estradiol may not be effective when given with a progestin. This was illustrated in a trial of 321 postmenopausal women in whom the combination of 17-beta-estradiol (1 mg/day) with a progestin (gestodene) produced no reduction in intima-medial progression after one year [35].

Data from one population-based, case-control study suggest a possible lower risk of myocardial infarction and stroke with esterified estrogens when compared with conjugated estrogens [36]. This observation has not been confirmed in clinical trials.

Secondary prevention — Although a number of observational and angiographic studies had strongly suggested that women with CHD derive the greatest benefit for prevention of subsequent coronary events and survival [37-41], clinical trial data have **not** confirmed these benefits [42-51].

The HERS-I trial was a randomized, blinded, placebo-controlled secondary prevention trial [42]. In this study, 2763 postmenopausal women under the age of 80 with a history of CHD were randomly assigned to receive the same regimen used in the WHI (0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate daily) or placebo for an average of four years [42]. Findings from this trial included:

- There was no significant difference between the two groups in the incidence of CHD events despite a net 11 percent decrease in serum LDL cholesterol concentrations and 10 percent increase in serum HDL cholesterol concentrations in the hormone cohort.
- More CHD events occurred in the hormone group during the first year of therapy, with a subsequent trend toward a reduction in risk in years 4 and 5.
- A post-hoc analysis of HERS-I did not identify any subgroup in which estrogen therapy was beneficial or harmful [47]. However, polymorphisms of platelet genes were reported to be predictors of CHD risk in a subsequent report [52].
- In another post hoc analysis, combined oral estrogen and progestin therapy appeared to reduce the risk of developing type 2 diabetes mellitus. However, this effect is insufficient to recommend HT as a diabetes prevention strategy in women with CHD. (See "Menopausal hormone therapy: Benefits and risks".)

The HERS-II trial was a continuation of HERS-I in which 93 percent of HERS-I participants enrolled in an unblinded follow-up study for 2.7 years [43]:

- The lower rates of CHD events in the estrogen–progestin group in years 4 and 5 did **not** persist in the follow-up years.

- Over the 6.8 years of HERS-I and HERS-II, continuous estrogen-progestin therapy did not reduce the risk of CHD events in women with established CHD (HR 0.99, 95% CI 0.84-1.14) (figure 3).

- There were no differences in women taking statins or aspirin.

Other data have confirmed the lack of efficacy of estrogen-progestin therapy for secondary prevention of CHD [15,45,46,48,49]. As examples:

- In a subgroup analysis of women with preexisting CHD in the WHI combined estrogen-progestin trial, subsequent risk of a CHD event was increased (HR 1.44, 95% CI 0.77-2.70), although the number of women in this group was small [15,17].

- In the Women's Angiographic Vitamin and Estrogen (WAVE) Trial, combined estrogen-progestin therapy (the same regimen as HERS and WHI) was associated with a nonsignificant worsening of coronary stenosis on angiography [49]. When patients with intercurrent death or myocardial infarction were included, a significant increase in coronary risk was seen. An antioxidant arm (vitamins C and E) of the trial also demonstrated possible harm.

  Unopposed estrogen and type of estrogen — Results from two trials suggest that neither unopposed estrogen nor a different type of orally administered estrogen is effective for secondary prevention of CHD, but an increase in CHD risk, as has been reported for combined estrogen-progestin therapy, has not been described.

  - In the WHI trial of unopposed estrogen, a subgroup analysis of 441 women with preexisting CHD suggested that the effect of estrogen versus placebo on CHD risk was similar to that seen in women with no documented CHD (HR 1.04 and 0.91 for women with or without previous CHD, respectively). The discrepancies in CHD risk between the unopposed estrogen trial and the combined estrogen-progestin trial suggest that the progestin played an important role in the increased CHD risk seen with combined therapy [20].

  - In the Esprit trial, there was no significant difference at two years between unopposed estradiol (estradiol valerate 2 mg) and placebo in the primary endpoint of reinfarction or cardiac death [50].

  - The Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) randomly assigned 226 postmenopausal women with established CHD to oral

micronized 17-beta-estradiol (1 mg/day) alone or with medroxyprogesterone acetate (5 mg daily for 12 consecutive days each month), or to usual care (control group) [51]. After a median of 3.3 years of follow-up, estradiol either alone or with sequentially added medroxyprogesterone acetate had no significant effect on progression of atherosclerosis as measured by quantitative angiography (increases of 2.2, 1.2, and 1.9 percent in the unopposed estrogen, combined estrogen-progestin, and control groups, respectively).

Transdermal estrogen — Transdermal estrogen has more favorable effects than oral estrogen on markers for cardiovascular risk [40], may be less thrombogenic [53], and may be associated with a lower risk of thromboembolism than oral estrogens (see 'Venous thromboembolism' below). However, there is no evidence to date that transdermal estrogen is safer for secondary prevention of CHD.

In the Papworth trial, 255 postmenopausal women with ischemic heart disease were randomly assigned to transdermal preparations (estrogen alone or combined with progestin) or placebo. After an average of 31 months of follow-up, there was a nonsignificant increase in coronary disease-related events in the transdermal MHT group when compared with placebo [54].

STROKE

The results of epidemiologic studies of estrogen therapy and stroke risk are conflicting. The findings range from a significant reduction of risk in the National Health and Nutritional Examination Survey (NHANES) (relative risk [RR] 0.37 after adjusting for other risk factors) [55], to no effect in a large case-control study [56], to an increase only in the first six months of therapy [57], to a slight increase in stroke risk in the Nurses' Health Study (RR 1.35) [11].

However, clinical trial data suggest that oral estrogen therapy **increases** stroke risk [58]:

- In the Heart and Estrogen/Progestin Replacement Study (HERS-I) trial of women with established coronary heart disease (CHD) described above, there was a strong trend toward an increase in risk for fatal stroke (RR 1.61, 95% CI 0.97-3.55) [59].

- In the Women's Estrogen for Stroke Trial (WEST), a double-blind, placebo-controlled trial in 664 postmenopausal women with established cerebrovascular disease, estrogen (oral estradiol 1 mg/day for an average of 2.8 years) had no effect on recurrent stroke or death (RR 1.0). Estrogen therapy did, however, increase the risk of fatal stroke (RR 2.9, 95% CI 0.9-9.0) [60]. In the Women's Health Initiative (WHI) trial, a 31 percent increase in stroke risk was seen with combined estrogen-progestin use compared with placebo (intention-to-treat hazard

ratio [HR] 1.31, 95% CI 1.02-1.68). The hazard ratios for ischemic and hemorrhagic stroke were 1.44 (95% CI 1.09-1.90) and 0.82 (95% CI 0.43-1.56), respectively [61]. The increased risk became evident between one and two years after randomization (figure 1) and was seen in all age groups. In the WHI trial of unopposed estrogen, stroke risk was significantly increased with conjugated equine estrogen versus placebo (HR 1.3, 95% CI 1.1-1.77) [16,62]. The excess risk of stroke was similar in women with or without previous stroke (HRs 1.67 and 1.39, respectively) [16]. In other subgroup analyses, the excess risk of stroke appeared to be present in women of all ages, including younger and recently menopausal women [62].

- In the follow-up analysis that combined the two WHI menopausal hormone therapy (MHT) trials (including 13 additional cases of stroke), stroke risk did not vary significantly by age or time since menopause (HR 1.32, 95% CI 1.12-1.56) [27]. However, the low baseline risk and modest HR in women ages 50 to 59 years resulted in no absolute excess risk in stroke (see 'Timing of exposure' above). Similar results were reported by the Nurses' Health Study [63].

- In a meta-analysis of randomized trials (including HERS, WEST, and WHI), oral estrogen therapy (with or without progestin) was associated with an increase in ischemic stroke but not hemorrhagic stroke or transient ischemic attacks (odds ratio [OR] 1.29, 95% CI 1.06-1.56 for ischemic stroke) [64]. In addition, among women who had a stroke, there was a trend towards more fatal stroke in those who were taking oral estrogen therapy.

Transdermal versus oral route — Low-dose, transdermal estrogen therapy does not appear to increase the risk of stroke in postmenopausal women. This was illustrated in a population-based, nested case-control study that included approximately 16,000 cases of stroke and 60,000 controls [65]. The overall rate of stroke in the cohort was 2.85 per 1000 per year. The risk of stroke was not increased in low-dose (≤50 mcg patch) transdermal estrogen users compared with nonusers (rate ratio 0.81, 95% CI 0.62-1.05), but was increased with higher transdermal doses (>50 mcg patch; 1.89, 95% CI 1.15-3.11). Current users of both low-dose (≤0.625 mg equine estrogens or ≤2 mg estradiol) and high-dose (>0.625 mg equine estrogens or >2 mg estradiol) oral HT had a higher rate of stroke than nonusers (rate ratio 1.28, 95% CI 1.15-1.42).

PERIPHERAL ARTERY DISEASE

Estrogen therapy does not appear to confer protection against peripheral artery disease. Although a population-based study suggested that estrogen therapy for one year or more was associated with a decreased risk of peripheral artery disease [66], this was not confirmed in the Heart and Estrogen/Progestin Replacement Study (HERS-I) trial described above in which therapy with estrogen and progestin did not significantly reduce the incidence of peripheral

arterial events, defined as carotid disease, abdominal aortic aneurysm, and lower extremity arterial disease (relative hazard 0.87 compared with placebo) [67].

In the Women's Health Initiative (WHI), which used a similar case definition for peripheral artery disease, combined conjugated estrogen-medroxyprogesterone acetate therapy neither favorably nor unfavorably affected risk of peripheral arterial events (hazard ratio [HR] 0.89, 95% CI 0.63-1.25) [68]. Data from the WHI unopposed estrogen trial are not yet available.

VENOUS THROMBOEMBOLISM

Observational studies, a small trial, and a meta-analysis published before the Women's Health Initiative (WHI) evaluated the association between estrogen therapy and venous thromboembolism (VTE) and suggested that hormone therapy (HT) caused approximately a twofold increase in VTE risk [69-74], particularly in women with the factor V Leiden mutation [75-77]. A limitation in interpreting these reports is that they had significant design limitations (eg, inconsistent or unreliable methods for diagnosing VTE, widely varying patient ages, lack of adjustment for confounding factors, and marked variations in estrogen preparation and dosing).

Women's Health Initiative — The most definitive clinical data come from the WHI trial and are consistent with previous estimates [78]:

- VTE risk was increased approximately twofold in the estrogen-progestin group compared with placebo (hazard ratio [HR] 2.06, unadjusted 95% CI 1.6-2.7). The increase in risk was similar for both deep vein thrombosis and pulmonary embolism, and it was particularly high in women with a previous event (HR 3.9).
- The rates of VTE were 3.5 and 1.7 per 1000 person-years in the estrogen-progestin and placebo groups, respectively.
- The increased risk was highest in the first year of therapy but persisted for the five years of follow-up (figure 2).
- Both older age and obesity were associated with additional excess risk, but the risk was not significantly altered by smoking, aspirin, or statin use.
- The presence of factor V Leiden further increased the risk of VTE in women receiving estrogen-progestin therapy compared with placebo (HR 6.7, 95% CI 3.1-14.5). Other genetic variants did not modify the risk of VTE with estrogen therapy. (See "Overview of the causes of venous thrombosis in adults".)

VTE risk in the WHI was also increased with unopposed conjugated equine estrogen when compared with placebo (HR 1.32, 95% CI 0.99-1.75) [79], which was lower than that seen in the combined estrogen-progestin trial [78]. The rate of VTE was 3.0 and 2.2 per 1000 person-years for unopposed estrogen and placebo, respectively [79].

A similar twofold increase in VTE risk with combined estrogen-progestin therapy was noted in the Heart and Estrogen/Progestin Replacement Study (HERS) trials [42]. There was a suggestion that risk was slightly decreased in women who also took daily aspirin (HR 1.68 and 4.23, unadjusted 95% CI 0.96-2.92 and 1.41-12.7 for aspirin versus no aspirin therapy, respectively).

In a systematic review and meta-analysis of 22 randomized trials of menopausal hormone therapy (MHT) (including both WHI trials), the risk of VTE was increased. After one year of use, the risk increased from 2 per 1000 to 2 to 10 per 1000 for combined estrogen-progestin therapy and to 4 to 11 per 1000 for unopposed estrogen therapy [32].

Mechanism — One possible mechanism for the increased VTE risk is an increase in activated protein C resistance that has been reported with both unopposed estradiol and combined estradiol-progestin therapy [80].

Type of oral estrogen — The type of oral estrogen used may affect VTE risk. As an example, in a population-based, case-control study of peri- and postmenopausal women ages 30 to 89 years (586 with venous thrombosis and 2268 healthy controls), women taking conjugated estrogens, but not esterified (plant-derived) estrogens, were at increased risk of VTE when compared with non-estrogen users (odds ratio [OR] 1.7, 95% CI 1.2-2.2 and 0.9, 95% CI 0.7-1.2, respectively) [81]. Among estrogen users, the risk was higher when combined with progestin compared with unopposed estrogen use (OR 1.6, 95% CI 1.1-2.3).

Route of estrogen — Transdermal estrogen, which has little effect on hemostasis, may be associated with a lower VTE risk. This was illustrated in a multicenter, case-control study in postmenopausal women that included 271 cases of VTE and 610 controls matched for age, center, and admission date [82]. The odds ratios for VTE in current users of oral or transdermal estrogen compared with nonusers were 4.2 (95% CI 1.5-11.6) and 0.9 (95% CI 0.4-2.1), respectively. In a prospective cohort study from the same investigators, neither medroxyprogesterone acetate nor micronized progesterone appeared to be associated with VTE risk, while norpregnane progestins (nomegestrol acetate and promegestone) were associated with excess risk [83].

In a meta-analysis that included the case-control study [82], as well as three others, no excess risk of VTE was observed in women taking transdermal estrogen (OR 1.2, 95% CI 0.1-1.7), even in those with prothrombotic mutations or high body mass index (BMI) [84]. Similar results were

reported in a population-based cohort study published after the meta-analysis [85]. The cohort included 23,505 cases of VTE matched with 231,562 controls. The risk of VTE was not increased with transdermal estrogen alone (relative risk [RR] 1.01, 95% CI 0.89-1.16) or combined with progestin (RR 0.96, 95% CI 0.77-1.20). In contrast, VTE risk was increased with current use of oral estrogen alone (RR 1.49, 95% CI 1.37-1.63), estrogen combined with a progestin (RR 1.54, 95% CI 1.44-1.65), and increased with estrogen dose. Risks were highest during the first year and disappeared four months after stopping therapy. There are currently no clinical trial data comparing the effect of transdermal and oral estrogen preparations on VTE risk.

Prothrombotic mutations — As noted in the WHI, the presence of factor V Leiden, but not other prothrombotic mutations, further increased the risk of VTE in women receiving estrogen-progestin therapy compared with placebo. In a case-control study of 235 postmenopausal women with documented VTE and 554 control subjects without VTE, transdermal estrogen, unlike oral estrogen, did not confer additional risk in women who carried a prothrombotic mutation [86].

Dose — Higher doses of estrogen, such as those used in oral contraceptives, may be associated with higher VTE risks when compared with MHT doses [87]. In addition, low-dose MHT (such as 0.3 mg conjugated estrogen) has fewer effects on coagulation and inflammatory markers than standard-dose therapy [88].

In summary, there is a small but significant increase in risk of thromboembolism with current HT, but for healthy postmenopausal women, the absolute risk is extremely low. Older age, obesity, and the presence of factor V Leiden may be associated with additional excess risk, but the risk does not appear to be altered by smoking, aspirin, or statin use.

Although thromboembolic risk may be affected by the type and dose of estrogen and the route of its administration, data are not yet sufficient to recommend one type of estrogen over another. Recommendations for MHT use are reviewed separately. (See "Treatment of menopausal symptoms with hormone therapy".)

Type of progestin — In addition to the type and route of estrogen administration, the type of progestin may also affect the risk of VTE. In a study of over one million postmenopausal women that included 2200 venous thromboembolic events, the relative risk of VTE in current hormone users versus nonusers was higher for women taking oral estrogen-progestin than unopposed estrogen regimens (RR 2.07 versus 1.42) [89]. Transdermal estrogen users had no excess risk. Among the oral estrogen-progestin users, risk was greater for regimens containing medroxyprogesterone acetate than other progestins (RR 2.67 versus 1.91).

The estimated absolute risk of being admitted to the hospital (or mortality from) pulmonary embolism was:

- 1 in 660 never users of HT
- 1 in 475 current users of oral estrogen-only HT
- 1 in 390 users of estrogen-progestin HT containing norethisterone/norgestrel
- 1 in 250 users of estrogen-progestin HT containing medroxyprogesterone acetate

LIPIDS

Oral estrogen has a proven beneficial effect on serum lipid concentrations [90-92], which can be negated in part by progestin therapy. One study, for example, randomly assigned women to treatment with 0.625 mg of conjugated equine estrogens or placebo [90]. Estrogen had the following effects on mean serum lipid concentrations:

- Low-density lipoprotein (LDL) cholesterol fell by 15 percent
- High-density lipoprotein (HDL) cholesterol increased by 16 percent
- Triglycerides increased by 24 percent

These effects appear to be independent of age, with similar results noted in women over age 74 years [92]. Estrogen may also lower lipoprotein(a) [Lp(a)] levels by approximately 20 percent [91,93,94]. (See "Lipoprotein(a)".)

The effect of oral estradiol (1 mg/day) is similar to that of oral conjugated equine estrogen, while **transdermal** estradiol has a lesser effect than oral estrogen preparations [90]. The lack of effect with transdermal estrogen presumably reflects decreased exposure of the liver to estrogen (compared with oral therapy) due to avoidance of the first-pass effect on the liver. However, another study which treated women for much longer with varying doses of transdermal estradiol found that the serum total and LDL cholesterol concentrations decreased in a dose-dependent fashion after two years of therapy [95].

Polymorphisms of the estrogen receptor-alpha (ER-alpha) gene may be associated with an augmented HDL cholesterol rise with estrogen therapy. In a study of 309 postmenopausal women with coronary disease participating in the Estrogen Replacement and Atherosclerosis (ERA) trial (see 'Secondary prevention' above), those with an IVS1-401 C/C genotype had a more significant increase in serum HDL cholesterol (limited to subfraction 3) with estrogen than other women (13.1 versus 6.0 mg/dL [0.34 versus 0.16 mmol/L], respectively, p = 0.04) [96]. There were similar changes in several closely related genotypes and in women receiving either unopposed estrogen or combined estrogen-progestin therapy. Thus, certain ER-alpha

polymorphisms may predict the serum HDL cholesterol response to estrogen therapy, but the clinical consequences of this effect are unknown. (See "HDL cholesterol: Clinical aspects of abnormal values".)

Women with hyperlipidemia — The preceding observations were made in healthy postmenopausal women. The effect of hormone replacement in women with hypercholesterolemia (baseline serum cholesterol concentration 305 mg/dL [7.9 mmol/L]) was evaluated in a study of 58 postmenopausal women randomly assigned to 1.25 mg conjugated estrogen with medroxyprogesterone acetate 5 mg/day or simvastatin (10 mg/day) in a crossover design (with an eight-week washout in between) [91]. Compared with simvastatin, menopausal hormone therapy (MHT) produced the following changes:

- A smaller decrease in total cholesterol – 14 versus 26 percent with simvastatin
- A smaller decrease in LDL cholesterol – 24 versus 36 percent
- A similar elevation in HDL cholesterol – 7 percent
- A reduction in Lp(a) – 27 percent versus no change with simvastatin
- An increase in triglycerides – 29 percent versus 14 percent decrease with simvastatin

One limitation of this trial is that the dose of conjugated estrogen used (1.25 mg/day) was twice the usual replacement dose. Nevertheless, the percentage changes in lipid values are similar to those seen in the other studies of postmenopausal women [90,93]. Furthermore, another trial of hypercholesterolemic postmenopausal women showed similar results when estrogen was compared with pravastatin [97]. In terms of serum LDL cholesterol, combination therapy appears to be better than estrogen alone but not better than a statin alone [97,98].

Hyperlipidemic women who are receiving combined cyclic estrogen-progestin therapy may have significant fluctuations in lipoprotein concentrations depending upon the phase of the cycle [99]. Thus, when considering lipid-lowering therapy, it is important to determine if this fluctuation is occurring in an individual woman and, if so, to consistently measure lipoproteins during the same hormonal phase (preferably the one which demonstrates the poorest results).

Because of a presumed cardioprotective effect and the above observations, estrogen was recommended in the past as first-line therapy for hyperlipidemia in women with coronary heart disease (CHD) [100]. However, this recommendation is no longer applicable because of the lack of cardiovascular protection noted in the Women's Health Initiative (WHI) and Heart and Estrogen/Progestin Replacement Study (HERS) trials [15,42,43,101]. Statins should be the first choice for lipid-lowering therapy in most women with CHD. (See "Management of low-density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease".)

Effect of progestins — A progestin is routinely administered with estrogen in women with an intact uterus to diminish the risk of endometrial hyperplasia cancer. (See "Menopausal hormone therapy: Benefits and risks".)

Progestins **attenuate** some of the beneficial lipid effects of estrogen. Both medroxyprogesterone acetate and levonorgestrel decrease serum HDL cholesterol by 8 to 18 percent [102]. However, the net effect of oral estrogen plus medroxyprogesterone acetate on serum HDL cholesterol is still beneficial, although not as beneficial as when estrogen is given alone [103,104]. Furthermore, addition of a progestin has little effect on the estrogen-induced reduction in serum LDL cholesterol (figure 2) [103-105].

The progestin in both the WHI and HERS trials was medroxyprogesterone acetate (2.5 mg/day). In the WHI, serum LDL cholesterol concentrations decreased, while serum HDL cholesterol and triglyceride concentrations increased more in the HT group than placebo (-12.7, +7.3, and +6.9 percent, respectively) [15].

In the WHI trial of unopposed estrogen (conjugated estrogen 0.625 mg/day), the changes in serum total, LDL, and HDL cholesterol concentrations were -2.3, -13.7, and +15.1 percent, respectively [16]. Serum triglyceride concentrations increased by 25 percent in the estrogen group. Further details of the WHI trials are found elsewhere. (See "Menopausal hormone therapy: Benefits and risks".)

Type of progestin — The type of progestin appears to be important with regard to serum HDL cholesterol. medroxyprogesterone acetate lowers serum HDL cholesterol much less than levonorgestrel [102], while oral micronized progesterone seems to have little or **no adverse effect** [102,103,106]. This issue was best addressed in the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial in which 875 women were randomly assigned to placebo or one of four treatment arms consisting of conjugated estrogen (0.625 mg/day) alone or with cyclic or continuous medroxyprogesterone or cyclic micronized progesterone (200 mg/day for 12 days per month) [103]. Serum HDL cholesterol concentrations rose by 5.6 mg/dL (0.14 mmol/L) with estrogen alone, 4.1 mg/dL (0.11 mmol/L) with estrogen plus micronized progesterone, and only 1.2 to 1.6 mg/dL (0.03 to 0.04 mmol/L) with medroxyprogesterone (figure 4). Estrogen, with or without progestin, reduced plasma Lp(a) levels by 17 to 23 percent [107].

Continuous versus cyclic combined regimens — A meta-analysis evaluated the results in over 300 women from six randomized, double-blind, clinical trials comparing continuous estrogen-progestin therapy (0.625 mg conjugated estrogens and 2.5 mg medroxyprogesterone, the most

commonly prescribed regimen in the United States) and cyclic therapy [108]. Overall, the effects were equivalent with the two regimens:

- A reduction in serum total cholesterol concentration of 14 to 15 mg/dL (0.36 to 0.39 mmol/L)
- A reduction in serum LDL cholesterol concentration of 17 to 18 mg/dL (0.44 to 0.46 mmol/L)
- An elevation in serum HDL cholesterol concentration of 2 to 3 mg/dL (0.05 to 0.08 mmol/L)

Effect on triglycerides — A potentially negative effect of estrogen therapy is its tendency to raise triglyceride concentrations by as much as 24 to 29 percent [90,91], although a smaller increase of 6.9 percent was noted in the WHI combined estrogen-progestin, but not the unopposed estrogen trial [15,16] (see "Hypertriglyceridemia in adults: Management"). Transdermal estrogen preparations do not raise triglycerides concentrations [108].

BLOOD PRESSURE

Replacement doses of estrogen have little effect on blood pressure. The Women's Health Initiative (WHI) combined estrogen-progestin trial noted only a small increase (1.5 mmHg) in systolic pressure compared with placebo [15]; a similar difference between the hormone and placebo groups of 1.1 mmHg was noted in the WHI trial of unopposed estrogen [16].

Similarly, the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial found that estrogen, with or without progestins, did not affect blood pressure [103]. These findings are in contrast to the frequent elevation in blood pressure seen when higher doses of estrogen are given for oral contraception. (See "Hormonal contraception in women with hypertension and other cardiovascular risk factors".)

BODY WEIGHT

Several reports suggest that the effect of estrogen on body weight is either neutral or slightly beneficial. A prospective, nonrandomized study of the Rancho Bernardo cohort of 651 women followed for 15 years found that estrogen therapy had no effect on body weight [109], while the randomized, placebo-controlled Postmenopausal Estrogen/Progestin Interventions (PEPI) trial found the women treated with estrogen gained significantly less weight than those treated with placebo [103]. A large osteoporosis prevention trial also reported that postmenopausal women receiving hormone therapy (HT) gained less weight than women receiving placebo [110].

Body fat distribution — Estrogen therapy also has a neutral or favorable effect on body fat distribution [109,111]. The pattern of regional fat distribution plays an important additional role

in the excess death associated with obesity. Abdominal obesity (also called upper body, male-type, android, or visceral obesity) is associated with an increased risk of hypertension, diabetes, and dyslipidemia compared with female-type or gynoid obesity, in which the excess weight accumulates in the femoral and gluteal regions. (See "Overweight and obesity in adults: Health consequences".)

The Rancho Bernardo cohort of 651 women found that body fat distribution was similar in women who did or did not take estrogen [109].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Menopause".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Menopause (The Basics)")
- Beyond the Basics topics (see "Patient education: Menopause (Beyond the Basics)" and "Patient education: Menopausal hormone therapy (Beyond the Basics)")

SUMMARY

- Although initial publications from the Women's Health Initiative (WHI) reported an excess risk of coronary heart disease (CHD) with combined estrogen-progestin therapy, secondary

analyses from the WHI data from a primate model, two observational studies in postmenopausal women, meta-analyses of clinical trials, and a coronary angiographic study all suggest that the excess CHD risk appears to be confined to older postmenopausal women or those who are >10 years postmenopause. This has been referred to as the "timing hypothesis." (See 'Timing of exposure' above.)

- In a combined analysis of the two WHI menopausal hormone therapy (MHT) trials, an increased risk of stroke was observed, that did not vary significantly by age or time since menopause (hazard ratio [HR] 1.32, 95% CI 1.12-1.56). However, the low baseline risk and modest HR in women ages 50 to 59 years resulted in no absolute excess risk in stroke. Low doses of transdermal estrogen do not appear to be associated with an excess risk of stroke. (See 'Stroke' above.)

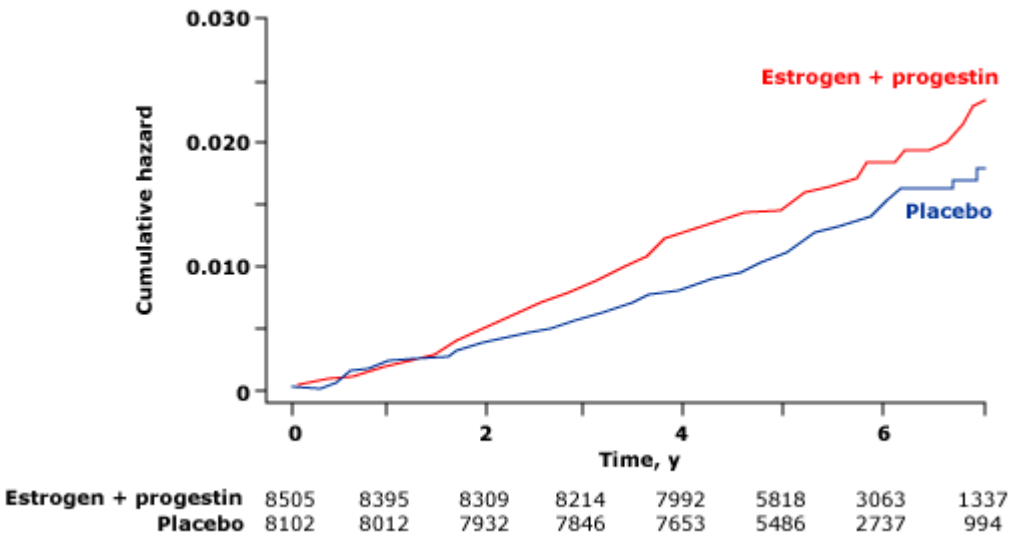
- There is a small but significant increase in risk of venous thromboembolism (VTE) with current hormone therapy (HT), but for healthy postmenopausal women, the absolute risk is extremely low. Transdermal estrogen preparations do not appear to be associated with excess risk. Older age, obesity, and the presence of factor V Leiden may be associated with additional excess risk. (See 'Venous thromboembolism' above.)

- The management of menopausal symptoms with HT is reviewed separately. (See "Treatment of menopausal symptoms with hormone therapy" and "Menopausal hot flashes".)

Topic 7409 Version 25.0

GRAPHICS

Women's Health Initiative: Risk of stroke

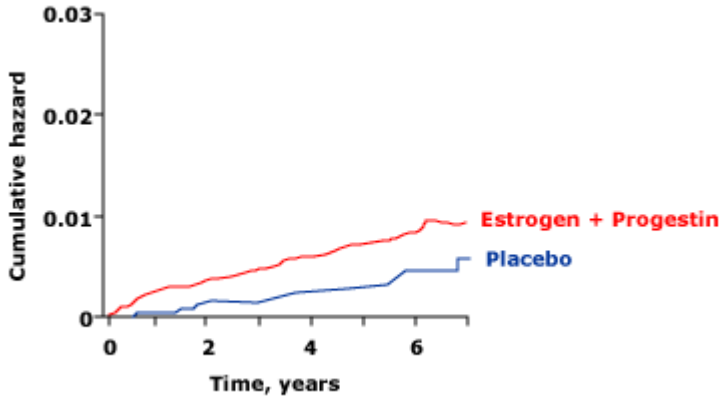


Kaplan-Meier estimates of cumulative hazard rates of stroke. In the Women's Health Initiative, combined estrogen-progestin therapy was associated with a significant increase in stroke when compared with placebo. The intention-to-treat hazard ratio was 1.31, 95% CI 1.02-1.68.

Data from: Wassertheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: The Women's Health Initiative: A randomized trial. JAMA 2003; 289:2673.

Graphic 74704 Version 4.0

HRT increases pulmonary embolism



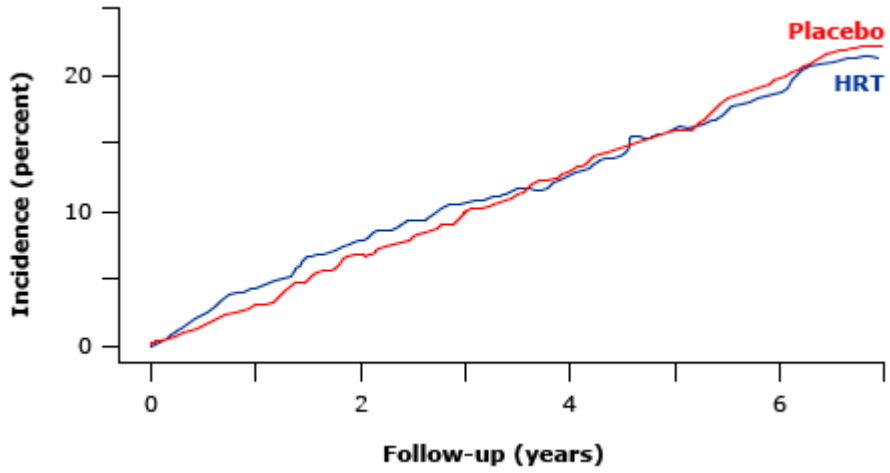
In the Women's Health Initiative, combined estrogen-progestin replacement therapy was associated with a significant increase in pulmonary embolism (eight more pulmonary emboli per 10,000 person-years; HR 2.13, unadjusted 95% CI 1.39-3.25).

HRT: hormone replacement therapy; HR: hazard ratio.

Data from: Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen and progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288:321.

Graphic 64173 Version 5.0

Estrogen therapy not beneficial for secondary prevention of coronary heart disease



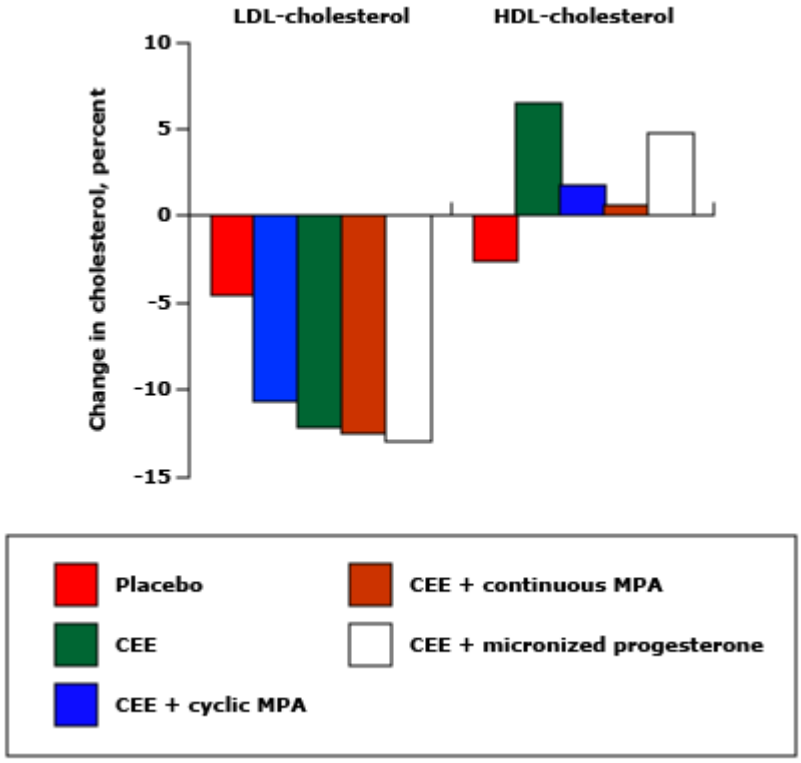
Data from the HERS-II trial on the incidence of coronary heart disease events (death or nonfatal myocardial infarction) in 2763 postmenopausal women with a prior history of myocardial infarction or interventional procedure who were treated with combined HRT or placebo. There was no difference between the two groups. The curves are truncated at year 7 when less than half of the cohort remained in follow-up.

HERS II: Heart and Estrogen/progestin Replacement Study follow-up; HRT: hormone replacement therapy.

Data from: Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA 2002; 288:49.

Graphic 62591 Version 6.0

Estrogen replacement therapy improves lipid profile



Effect on serum LDL and HDL cholesterol concentrations of placebo or four hormone replacement regimens in postmenopausal women: CEE alone, with either cyclic or continuous MPA, or with micronized progesterone. CEE had the favorable effects of lowering serum LDL cholesterol and raising HDL cholesterol concentrations. The effect on serum LDL cholesterol was not changed with addition of a progestin (left panel), but only micronized progesterone caused an equivalent elevation in serum HDL cholesterol (right panel).

CEE: conjugated equine estrogens; LDL: low-density lipoprotein; HDL: high-density lipoprotein; MPA: medroxyprogesterone acetate.

Data from: Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial, JAMA 1995; 273:199.

Graphic 65403 Version 2.0